PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100985-1 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/002702	International filing date *(day/month/year)* 23.06.2004	Priority date *(day/month/year)* 27.06.2003
International Patent Classification (IPC) or national classification and IPC C07D239/46, C07D401/12, C07D405/12, C07D309/04, C07D295/22, A61K31/496, A61P11/00, A61P19/02		
Applicant ASTRAZENECA AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2004	30.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 7818 Schumacher, M.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002702

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-45 as originally filed

   Claims, Numbers

   1-31 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-24 (all part.), 25-27

because:

☒ the said international application, or the said claims Nos. 25-27 for industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 16-24 for the term "prodrug" are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-24,28-31
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Claims 16-24 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined:
These claims refer to the term "prodrugs". "prodrugs" is a functional definition which attempts to define a chemical compound in terms of a result to be achieved. This is not allowable (Article 6PCT). On p.13, l.15-16 of the description the definition of the term "prodrug" refers to "compounds which are hydrolysed *in vivo* to form compound of formula (I)". This definition could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out over the whole claimed area without imposing an undue burden, the disclosure may be considered insufficient in the sense of Article 6 PCT. This term "prodrug" should therefore be deleted from the scope of claims 16-24.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 **The following documents are referred to in this communication:**

D1: WO 00/75108 A1 (ASTRAZENECA UK LIMITED, UK; ZENECA-PHARMA S.A.) 14 December 2000

D2 : WO 03/014092 A1 (ASTRAZENECA AB, SWED.) 20 February 2003

D3: WO 00/12478 A1 (ZENECA LTD, UK; ZENECA-PHARMA SA) 9 March 2000

D4: WO 01/62742 A1 (ASTRAZENECA AB, SWED.; ASTRAZENECA UK LIMITED) 30 August 2001

D5: WO 99/38843 A1 (DARWIN DISCOVERY LIMITED, UK) 5 August 1999

2. **NOVELTY, ARTICLE 33(1) AND ARTICLE 33(2) PCT:**

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the compounds of formula (I) according to current claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The compounds of D4 differ from those claimed because the ring B is never substituted by an alkoxy or an aryloxy substituent.
The subject-matter of claim 1 is totally included in the generic disclosure of compounds of D1-D3 and D5 (see respectively claim 1 of D1-D3 and D5). However, none of these documents contain specific examples of compounds falling within the scope of present claim 1; thus, the subject-matter of the present invention could be considered as a novel selection of the compounds of D1-D3 and D5 and the selection consists mainly in choosing an alkoxy or an aryloxy as substituent of the ring B.

3 INVENTIVE STEP, ARTICLE 33(3) PCT:

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claim 1 does not involve an inventive step in the sense of Article 33(3)PCT.
Documents D1-D3, directed to metalloproteinases inhibitors, in particular MMP13, are considered as the closest prior art documents. Since the present application can be considered as a novel selection of these documents, the technical problem underlying the present invention has to be seen in the provision of MMP13 inhibitors which have an unexpected advantageous effect in comparison with the compounds of D1-D3.
The pharmacological data on p.18 the present application show that the claimed compounds indeed possess a metalloproteinase inhibitory activity but there is no evidence that prove that they possess an unexpected improved effect compared to the MMP13 inhibitors of D1-D3. In fact, at the present stage there is no appropriate information to clarify which unexpected effect is associated with the selection of an alkoxy or aryloxy substituent on the B ring of the compounds of D1-D3.
Thus, in the absence of evidence of such advantages, Article 33(3) PCT cannot be considered to be satisfied.

4. INDUSTRIAL APPLICABILITY:

For the assessment of the present claims 25-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.